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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/549,867

09/22/2005

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EXAMINER

WANG, CHANG YU

ART UNIT

PAPER NUMBER

1649

MAIL DATE

DELIVERY MODE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/549,867	Applicant(s) STEER ET AL.	
	Examiner Chang-Yu Wang	Art Unit 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 4/27/09.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-3,7,8,15-17,66,67 and 78 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3,7,8,15-17,66,67 and 78 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

RESPONSE TO AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/27/09 has been entered.

Status of Application/Amendments/claims

2. Applicant's amendment filed 4/27/09 is acknowledged. Claims 4-6, 9-14, 18-65, 69-77 and 79-80 are cancelled. Claim 1 is currently amended. Claims 1-3, 7, 8, 15-17, 66-68 and 78 are pending in this application.

3. Claims 1-3, 7, 8, 15-17, 66, 67 and 78 are under examination with respect to an ***in vitro*** method of making a transplant cell population and promoting its viability by ***in vitro*** treatment of cells with ursodeoxycholic acid (UDCA) or its analog in this office.

4. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

5. Applicant's arguments filed on 4/27/09 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Withdrawn

6. The rejection of claims 1-2, 4, 7-8, 15-19, 66-68 and 77-78 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in response to Applicant's argument on p. 6 of the response.

The rejection of claims 1-4, 7, 8, 15-17, 66, 67, 77 and 78 under 35 U.S.C. 102(b) as being anticipated Rodrigues et al. (Journal of Neurochemistry. 2000, Vol. 75, pages 2368-2379, as in IDS) is withdrawn in response to Applicant's amendment to the claims by reciting "human".

The rejection of claims 1-4, 7, 8, 15-17, 66, 67, 77 and 78 under 35 U.S.C. 102(b) as being anticipated by Silva et al. ("Bilirubin induced apoptosis in rat cultured neural cells is aggravated by chenodeoxycholic acid but prevented by ursodeoxycholic acid". Journal of Hepatology. 2001, Vol. 34, pages 402-408) is withdrawn in response to Applicant's amendment to the claims by reciting "human".

The rejection of claims 1-4, 7, 8, 15-17, 66, 67, 77 and 78 under 35 U.S.C. 102(b) as being anticipated by Duan et al. (Cell Transplantation. 2002, vol. 11, pages 195-205) is withdrawn in response to Applicant's amendment to the claims by reciting "human".

Claim Rejections/Objections Maintained

In view of the amendment filed on 4/27/09, the following rejections are maintained.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 is indefinite because the claims recite both narrow and broad limitations. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 3 recites the broad recitation "pluripotent stem cells, embryonic stem cells, adult stem cells and combination thereof" amino acids residues 28-299 of SEQ ID NO:3, and the claim also recites "precursor

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cells of dopamine neurons", which is the narrower statement of the range/limitation because precursor cells of dopamine neurons are the cell lineage derived from pluripotent, embryonic or adult stem cells. Thus, the claim is indefinite.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-3, 7, 8, 15-17, 66, 67 and 78 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Duan et al. (Cell Transplantation. 2002, vol. 11, pages 195-205) in view of Falasca et al. (Transplantation. May 2001, Vol. 71, No. 9, pages 1268-1276, as in IDS) Rodrigues et al. (Journal of Neurochemistry. 2000, Vol. 75, pages 2368-2379, as in IDS), and Silva et al. (Journal of Hepatology. 2001, Vol. 34, pages 402-408). The reference of Duan (Society for Neuroscience Abstracts, 2001, vol. 29, p. 1245) is withdrawn. The rejection is maintained for the reasons made of record.

Claims 1-3, 7, 8, 15-17, 66, 67 and 78 as amended, are directed to a method of promoting viability of a transplant cell population comprising *in vitro* treatment of cells with ursodeoxycholic acid (UDCA) or its salts or its analog wherein the cells are human dopamine neurons or precursors thereof and wherein the cells are from autologous, heterologous or xenologous tissues (claims 16-17). Some claims are further drawn to contacting the cells with UDCA or its analog in combination with pharmaceutically

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acceptable carrier. Some claims are further drawn to contacting the cells with the UDCA analog such as tauroursodeoxycholic acid (TUDCA) (claim 67). Some claims are further drawn to cells being pluripotent, embryonic, adult stem cells (claims 3 and 78), or human embryonic ventral mesencephalic cells (claim 68).

On p. 10-11 of the response, Applicant argues that none of the cited references teach the claimed method of promoting viability pertaining to cells of a human transplant cell population which are human dopamine neurons or precursors thereof. Applicant argues that Falasca pertains to treatment of human liver cells with TUDCA, and Rodrigues and Silva pertain to rat cells and do not mention human dopamine neurons. Applicant further argues that Duan (Soc, Neurosci Abstracts; Duan I) and Duan (Cell transplantation; Duan II) does not teach a method of pertaining to cells of a human transplantation cell population which are dopamine neurons or precursors thereof as currently claimed. Applicant argues that there is no motivation to combine the applied references to reach the claimed invention. Applicant's arguments have been fully considered but they are not persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In addition, only a reason, suggestion or motivation need appear in the cited prior art in order to combine references under 35 U.S.C. 103. *Pro Mold Tool Col. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996).

The motivation to combine can arise from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. MPEP. §2144.07.

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involve not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See *CTS Corp. v. Electro Materials Corp. of America* 202 USPQ 22 (DC SNY 1979); and *In re Burckel* 201 USPQ 67 (CCPA 1979).

Furthermore, it is not necessary that the claimed invention be expressly suggested in any one or all of the references to justify combining their teachings; rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

In this case, in contrast, the examiner asserts that the applied references do render the claimed invention obvious. Briefly, Duan teaches a method of promoting cell viability of neural grafts when cells are transplanted into the brain (see p. 195, abstract, in particular). Duan teaches that transplantation of human embryonic dopamine neurons in patients with Parkinson's disease (PD) has demonstrated some success and are

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under clinical trial (p. 195; p. 204, in particular) and also teaches a method of promoting viability of dopamine neurons in a transplant cell population (neural grafts isolated from embryonic ventral mesencephalons, which contain pluripotent and embryonic stem cells as in claims 3, 68 and 78) wherein the cultured dopamine neurons containing differentiated dopamine neurons or dopamine precursors cells are treated with tauroursodeoxycholic acid (TUDCA) as in claims 1, 2 (see p. 195, abstract; p. 196 1st col., 2nd paragraph & 2nd col. , 2nd paragraph; p. 199-200, in particular). Duan further teaches that supplemental addition of TUDCA during the preparation of cell suspensions increases the survival of neural graft (see p. 203, 1st col., in particular). Duan teaches that the majority of transplanted dopamine neurons die immediately following transplantation, and that transplantation of a large number of transplanted dopamine neurons results in a more pronounced clinical improvement (p. 203, 2nd col.- p. 204, 1st col. in particular). Thus, a skilled artisan would be motivated to use TUDCA to promote cell survival (viability in a transplant cell) of dopaminergic neurons or precursor while preparing dopaminergic neurons or precursor from embryonic ventral mesencephalons (midbrain for isolating dopaminergic neurons) for neural transplantation in patients with PD.

Although, Duan does not explicitly teach human cells, Duan teaches that transplantation of human embryonic dopamine neurons in patients with Parkinson's disease has demonstrated some success and are under clinical trial (p. 195, in particular) and Falasca teaches a protective role of tauroursodeoxycholate (TUDCA which is UDCA analog) during harvesting and cold storage of human tissue as intended

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for transplantation (see p. 1268, abstract; p. 1269, col. 2, paragraph 5, in particular).

Thus, based on the teaching of Duan in combination with the teaching of Falasca, a skilled artisan would have been motivated to improve the survival of transplanted dopaminergic neurons or precursors preparing human embryonic dopaminergic neurons in the presence of UDCA or TUDCA to promote the viability of the transplanted dopamine neurons or precursors; and thereby to further improve PD.

Although Falasca does not teach dopamine neurons or precursors thereof, Silva, Rodrigues, and Duan teach a method of promoting viability of dopamine neurons or precursors thereof for transplantation by UDCA or TUDCA. In particular Silva teaches that UDCA and its conjugated derivative TUDCA prevents cell death of neuronal cells isolated from the ventral mesencephalic region of embryonic rat brains (page 403, col. 2, par. 2), which the region for isolating dopaminergic neuron precursors (see page 403, col. 2, par. 2; Fig. 4; page 406, col. 1, lines 6-9, in particular). Rodrigues teaches that TUDCA prevents apoptosis in of neuronal cell populations RN33B (see p. 2368, abstract; p. 2369, col. 2, paragraph 3; Fig. 1; Fig. 7, in particular) and RN33B are neuronal progenitor cells derived from embryonic rat raphe nuclei or from midbrain section (mesencephalon) as evidenced by Onifer et al. (see abstract). Duan teaches a method of promoting viability of dopamine neurons wherein the method comprises one active step of *in vitro* treatment of the dopamine neurons cells with tauroursodeoxycholic acid (TUDCA) wherein the dopamine neurons are prepared from embryonic ventral mesencephalon of rats (entire document including abstract). The

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teaching of Duan in combination with the teachings of Falasca, Silva and Rodrigues do render the claimed method obvious. Note that

“Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. *In re Kahn*, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006)” See MPEP § 2143. 01-I.

“It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art.” *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980); see also *In re Crockett*, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) and *Ex parte Quadranti*, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992). See MPEP § 2144.06.

“The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)”. See MPEP § 2144.07.

On p. 11 of the response, Applicant argues that the examiner applied an inappropriate level of hindsight and over-reaches field of endeavor to piece the teachings of the cited references. Applicant’s arguments have been fully considered but they are not persuasive.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the

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art would be reasonably be expected to drawn therefrom. *In re Preda*, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968).

In addition, the examiner asserts that the cited references are in the same field of endeavor (i.e. the use of UDCA and its analogs for in promoting cell viability *in vitro*) and they seek to solve the same problems as the instant application and claims (such as protection of mammalian cells from apoptosis as intended for further transplantation), and one of skill in the art is free to select components available in the prior art, *In re Winslow*, 151 USPQ 48 (CCPA, 1966).

Conclusion

9. NO CLAIM IS ALLOWED.

10. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/

Chang-Yu Wang, Ph.D.

June 25, 2009

/Christine J Saoud/

Primary Examiner, Art Unit 1647